# How generalizable to community samples are clinical trial results for treatment of nicotine dependence: A comparison of common eligibility criteria with respondents of a large representative general population survey

Yann Le Strat, Jürgen Rehm, Bernard Le Foll

# How generalizable to community samples are clinical trial results for treatment of nicotine dependence: A comparison of common eligibility criteria with respondents of a large representative general population survey

Yann Le Strat[1,2,3,4,5], Jürgen Rehm[6,7,8,], Bernard Le Foll[1,2]

Centre for Addiction and Mental Health, Toronto, CANADA

[1] Translational Addiction Research Laboratory, Centre for Addiction and Mental Health, Toronto, Ontario, Canada.

[2] Addiction Program, Centre for Addiction and Mental Health, Toronto, Ontario, Canada

[3] INSERM U894, Team 1, Centre for Psychiatry and Neurosciences, 2 ter rue d'Alesia, 75014, Paris, France.

[4] Department of Psychiatry, Louis-Mourier Hospital, AP-HP, Colombes, France.

[5] Faculty of Medicine, University Paris 7 Denis-Diderot, Paris, France.

[6] Centre for Addiction and Mental Health (CAMH), Toronto, Canada

[7] Dalla Lana School of Public Health (DLSPH), University of Toronto, Canada

[8] Institute for Clinical Psychology and Psychotherapy, TU Dresden, Germany

**Abstract**

**Objectives:** To examine the generalizability of findings from clinical trials of individuals with nicotine dependence to a large general population sample.

**Methods:** Eligibility criteria were drawn from typical criteria of clinical trials for nicotine dependence. The National Epidemiological Survey on Alcohol and Related Conditions (NESARC), a large national sample of the United States population, was used to assess how many potentially eligible people would fulfil the eligibility criteria. NESARC interviewed more than 43,000 adults aged 18 years and older. We applied a standard set of eligibility criteria representative of smoking cessation clinical trials to all the 4,962 adults with past 12 months nicotine dependence, and then to a sub-group of participants motivated to quit (n=4,121).

**Results:** We found that approximately 6 out of ten participants (65.89%) with nicotine dependence were excluded by at least one criterion. In the sub-group of nicotine dependent participant motivated to quit, more than half (58.60%) were excluded by at least one criterion. For the overall sample, smoking 10 cigarettes per day or less and lack of motivation to quit were the two criteria leading to exclusion for the greatest percentage of individuals (32.02% and 17.60 % respectively). For the sample motivated to quit, smoking less than 10 cigarettes per day or less and current depression led most frequently to exclusion (33.79% and 15.71% respectively).

**Conclusions:** Further studies and interventions should explore efficacy of tobacco treatment interventions in larger segment of the population, notably on the subpopulations of people with nicotine dependence who smoke less than 10 cigarettes per day or with comorbid depression.

**What this paper adds**

Clinical trials for treatment of nicotine dependence often exclude sizable parts of the general population with nicotine dependence. This article quantifies the lack of generalizability by using a large representative US general population survey. It was found, that the majority of nicotine dependent subjects would have been excluded from participating in clinical trials.

Clinical guidelines are developed based on the evidence obtained using clinical trials [1-4]. In smoking cessation trials, exclusion and eligibility criteria are highly used in order to maximize treatment efficacy and safety [5]. However, they may impair the external validity of the study, since they often exclude a substantial proportion of participants, resulting in a selection bias [5], and extending the gap between research and clinical practice [6]. Common exclusion criteria include age, current or past psychiatric/drug disorder, minimal levels of tobacco use and medical conditions [7]. There is a risk that this selection of the participants involved affects the results of the treatment trial for nicotine dependence as it is the case in other domains [8, 9]. The impact of eligibility/exclusion criteria on the generalizability of clinical trials has been described for antidepressant efficacy trials [5, 10-14], antipsychotic efficacy trials [15-17] and clinical trials for alcohol dependence [18-21] and cannabis dependence [22]. The percentage of subjects excluded by these criteria ranged between 50.5% and 75.8% in these studies [10, 18].

The impact of eligibility criteria in smoking cessation trials has been discussed in the literature [7, 23-29]. As called by CONSORT guidelines, several studies reported the reasons for ineligibility [7, 28]. For example, Robinson *et al.* screened 1,347 adolescents for a nicotine replacement treatment trial, and found that only 24.4% were eligible for inclusion in the trial [28]. The main reason for ineligibility was a failure to meet minimum requirement regarding the number of cigarettes smoked per day and/or a low level of nicotine dependence (criterion present in 39.1% of ineligible individuals) [28]. More recently, Kamholtz *et al.* assessed 97 non-eligible and 201 eligible participants in a laboratory research on smoking [7]. They reported that the main reasons for ineligibility were current alcohol and substance use disorders (present in 23.7% and 11.3% of ineligible individuals respectively) and failure to meet minimum requirement regarding cigarettes smoked per day (24.7%). However, when

comparing eligible and non-eligible participants, they found no difference in levels of nicotine dependence as assessed by the Fagerström Test for Nicotine Dependence Questionnaire [30].

A limitation of the clinical trials reported in the literature is that they rely on a sample of participants, and therefore cannot be extrapolated to individuals with nicotine dependence in the community. As suggested by Robinson *et al.*[28], and in order to understand the impact of eligibility criteria in the population, an analysis of the application of eligibility criteria to a representative general population sample of individuals with nicotine dependence is required. In that view, we assessed the effect of exclusion criteria commonly applied in clinical trials in a large, nationally representative sample, the National Epidemiological Survey on Alcohol and Related Conditions (NESARC). The NESARC is a survey conducted in the United States, including a broad range of psychiatric disorders as well as measures of various medical conditions. We used a method previously described by Blanco *et al.* in clinical trials for major depression [10] and alcohol dependence [18]. We wanted to estimate the population generalizability of clinical trials for nicotine dependent individuals. We applied common clinical trial eligibility criteria to all individuals with a current diagnosis of nicotine dependence, and then to a subsample of individuals who were motivated to quit, to examine proportion who would have been excluded in treatment trials for nicotine dependence.

## Methods

### Participants

Subjects were participants in NESARC, a nationally representative face-to-face survey of 43,093 respondents aged 18 years and older (response rate, 81%), conducted by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in 2001–2002 [31, 32]. The NESARC assessed the civilian non-institutionalized population residing in the United States. African-

Americans and Hispanics were oversampled, as were young adults. The research protocol, including informed consent procedures, received full ethical review and approval from the US Census Bureau and the Office of Management and Budget. Data were adjusted for oversampling and household- and person-level nonresponse. The weighted data were then further adjusted to represent the civilian population in the United States based on the 2000 Census.

## Measure of Nicotine Dependence

The NESARC used the National Institute on Alcohol Abuse and Alcoholism's Alcohol Use Disorder and Associated Disabilities Interview Schedule DSM-IV version (AUDADIS-IV), a structured diagnostic interview made for non-clinician interviewers [33]. Algorithms were designed to produce diagnoses of nicotine dependence consistent with the final DSM-IV criteria. For example, the "using nicotine to relieve or avoid withdrawal symptoms" criterion was defined by the following 4 items: (1) the use of nicotine as soon as waking up, (2) the use of nicotine after being in a situation in which use was forbidden, (3) the use of nicotine to decrease nicotine withdrawal symptoms, and (4) waking up in the middle of the night to use tobacco [34]. Several studies have documented good to excellent retest reliability [35].

## Data Analysis

Exclusion criteria commonly applied in clinical trials of treatments for nicotine dependence (see below in Clinical Trial Exclusion Criteria) were applied to individuals from the general population to determine the proportion of individuals from the general population with current nicotine dependence according to DSM-IV criteria that would be eligible for the clinical trials. The same criteria were applied to the subset of individuals with current nicotine dependence motivated to quit, examining potential differences in eligibility between motivated and less

motivated individuals, using a pattern of analysis described elsewhere [10, 18]. In these studies, Blanco *et al.* used attempts to quit a substance in the last 12 months as a proxy variable for motivation to quit in the future [10, 18].

The appropriate statistical weight was employed when mentioned to ensure the data were representative of the population.

## Clinical Trial Exclusion Criteria

We examined eligibility criteria from clinical trials included in a recent meta-analysis comparing the effectiveness of pharmacotherapies for smoking cessation [36]. We collected all eligibility criteria from 54 randomized clinical trials [37-92], and ranked them according to their frequency. Criteria included in more than 10% of the studies are listed in Table 1. The median of the number of eligibility criteria used in a study was 12 (considering not only criteria included in Table 1 but also criteria present in less than 10% of the studies). We thus applied the 12 most frequently used criteria to the NESARC sample.

The percentages of individuals excluded by criteria 1, 3, 5, 6, 7, 8, 11 and 12 were estimated from data collected by the AUDADIS-IV. Information to approximate criterion 4 (use of psychotropic medications), criterion 9 (use of bupropion or nicotine replacement therapy) and criterion 10 (history of eating disorder) was not available in the NESARC.

Criterion 1 (pregnancy status) was assessed with a single question ("Were you pregnant at any time during the past year?").

The presence of a recent cardiac event (criterion 2) was assessed by series of questions on chest pain, angina pectoris, heart attack, myocardial infarction or any other form of heart disease in the last 12 months, and whether the diagnosis was confirmed by a physician.

Criterion 3 ("Smoking 10 cigarettes per day or less on average ") was applied using a 12-month time frame (as it is assessed in the NESARC).

Criterion 5 (“Alcohol dependence “) was defined having a diagnosis of alcohol dependence within the last 12 months.

Criterion 6 (“Being not motivated to quit smoking “) was assessed by 2 questions: “In you entire life, did you ever, more than once, want to stop or cut down your tobacco use?”), and “Did this happen in the last 12 months?”. Participants who respond positively to both questions were classified as being motivated to quit smoking. Other participants were classified as being not motivated to quit smoking. This assessment is therefore at variance with standard questions about motivation in research trials, who usually asked whether participants want to cut down/attempt to stop in the future rather than if they have done so in the past.

Criterion 7 (“Dependence to other drugs”) was defined having a diagnosis of dependence to an illicit substance (either sedatives, tranquilizers, opiates, stimulants, hallucinogens, cannabis, cocaine (including crack cocaine), inhalants/solvents, heroin, or other drugs) within the last 12 months.

Criterion 8 (“Having a current depression”) was assessed using the criteria for Major Depressive Disorder within the last 12 months.

Criterion 11 (“Having a current psychosis”) was assessed by 2 questions: “Did a doctor or other health professional ever diagnose you with schizophrenia or psychotic illness or episode?”. Participants who respond positively to this were classified as having “psychosis”.

Participants with a lifetime history of mania were classified as having a bipolar disorder (Criterion 12). We choose to consider only bipolar type I disorder because hypomania, the hallmark of bipolar type II disorder, is a more subtle form of the disorder and therefore not likely to be screened in routine in eligibility assessments of clinical trials for nicotine dependent individuals. For the same reason, we considered participants as having bipolar disorder if they had a history of mania even if manic episodes were induced by a substance or

an illness, and did not restricted our analysis to independent bipolar disorders. As a control, we did a sensitivity analysis to examine how the results would change if (i) substance and illness induced mania were ruled out, and (ii) if bipolar type II disorder was also included in the eligibility criteria (with substance and illness induced disorders being ruled out).

Analysis Plan

We first determined the number and percentage of nicotine dependent participants of the NESARC who would be excluded by individually applying each of the 12 most frequent eligibility criteria reported previously. . Because individuals might have been excluded by more than 1 criterion, we also calculated the overall percentage of subjects who would have been excluded by the simultaneous application of all the measurable criteria. We conducted these analyses for all individuals with a current DSM-IV diagnosis of nicotine dependence (n=4,962), and for the sub-sample of individuals who want to stop or cut down on tobacco use in the last 12 months (n=4,121). Weighted prevalence estimates and 95% confidence intervals were computed using SUDAAN, version 10.01 (Research Triangle Park, NC). This software implements a Taylor linearization to adjust for complex survey sampling design effects including clustering data.

**Results**

The percentage of subjects excluded by at least one criterion was 65.89% among respondents who met DSM-IV criteria for nicotine dependence and 58.60% of those motivated to quit smoking in the past year (Table 2)

The percentage of respondents excluded due to the application of a single criterion ranged from 2.14% (lifetime diagnosis of psychosis) to 32.02% (smoking less than 10 cigarettes per

day) in the overall sample of respondents with nicotine dependence, and 1.95% (lifetime diagnosis of psychosis) to 33.79% (smoking less than 10 cigarettes per day) among those motivated to quit smoking.

For the overall sample, smoking 10 cigarettes per day or less and lacking motivation to quit were the two criteria including the highest percentage of individuals. For the treatment-seeking sample, having a current depression and smoking 10 cigarettes per day or less were the criteria comprising the greatest percentage of individuals who would not be eligible. Current alcohol dependence and a history of bipolar disorder also excluded a notable proportion of individuals in both samples (Table 2).

A history of bipolar disorder (type I) was present in 10.33 % of the participants with nicotine dependence (CI 95%: 8.16-10.50). As a control, ruling out illness- and substance-induced mania only slightly decreased to 9.26% the percentage of participants excluded because of this criteria (CI 95%:8.16-10.50). When bipolar type II disorder was also included in this eligibility criteria (substance- and illness-induced disorder still ruled out), the percentage of participants excluded because of this criteria raised to 14.70% (95%CI: 13.55-15.93). The overall exclusion rate was 65.58% when considering bipolar I disorder after ruling out illness and substance induced mania, and 66.8% when considering bipolar I and II after ruling out illness and substance induced mania, compared to an overall exclusion rate of 64.13% when considering only bipolar I disorder even if manic episodes were induced by a substance or an illness. This suggests that the criteria used to define bipolar disorder have little or no impact on the overall inclusion rate.

More than 6 out of ten respondents from the full nicotine dependent sample and more than half of the subsample of individuals motivated to quit smoking would have been excluded by one or more of the study criteria.

## Discussion

This study ascertains the proportion of community-dwelling adults with nicotine dependence that would have been eligible for a typical nicotine dependence treatment study. The results of this study suggest that traditional criteria used in nicotine dependence trials tend to exclude from participation half of individuals with nicotine dependence who are likely to seek out a treatment. These results are in line with previous findings, suggesting that a majority of individuals who were screened for a nicotine cessation trail were not eligible to participate to the trial. For example, among the 54 randomized clinical trials assessed in the present paper [37-92], the ineligibility rates varied widely, ranging from 12.9% [37]to 85.31[56]..

Consistent with the existing literature, we found that a lack of motivation to quit and a low level of cigarette consumption explain a large proportion of ineligibility [7, 28].

Our study has several limitations.

First of all, our exclusion criteria are somehow arbitrary. ,We considered eligibility criteria from 54 randomized clinical trials included in a recent meta-analysis [36], but the use of another methodology could have led to other results. An important point is that the exclusion criterion based on alcohol consumption varies widely across studies. It has been emphasized that an alcohol-related exclusion criterion appears frequently in smoking cessation pharmacotherapy trials [29, 93]. A recent review showed that 41.6% of trials (45 of 125 nicotine replacement trails, 15 of 22 bupropion trials and 3 of 3 varenicline trials) involved exclusion of participants with either current or recent alcohol problems, leading to a lack of information on the effects of alcohol use disorders on smoking cessation [29, 93].

A second restriction is that 3 of the 12 exclusion criteria initially included could not be operationalized in our study, because the relevant information was not assessed in the

NESARC sample, including (1) participants currently taking a psychotropic medication, (2) participants "currently taking Bupropion or nicotine replacement therapy", and (3) having an eating disorder,. This may theoretically lead to an underestimation of the proportion of patients excluded in clinical trials. However, these criteria are rarely met in the general population. For example, the estimated percentage of smokers in Australia who used bupropion in a year was only 3.6% in 2005 [94]. Eating disorders have a low prevalence, affecting less than 4.5% [95] of the general population. While an investigation of the impact of these exclusion criteria on the generalizability of clinical trials is required in a future study, they are not likely to exclude a significant proportion of smokers.

A third limitation is that the NESARC sample included only individuals aged 18 years or older. Information was unavailable for adolescents, who may be have a lower level of comorbidities, and may therefore be more likely to be eligible for clinical trials.

Some of the criteria have been implemented for safety reasons (e.g pregnancy, potential interaction with psychotropic drugs or with alcohol) while some other may contribute to stigmatize a significant proportion of the population (e.g having a history of substance abuse with no use within the last 12 months should not be considered as valid exclusion criteria in a clinical trial).

The exclusion of participant with alcohol dependence is particularly damageable, since nicotine dependence is a major issue in alcohol-dependent patients. For example, smokers with a lifetime history of alcohol dependence are more likely to die of smoking-related diseases rather than from alcohol-related diseases [96]. Moreover, alcohol-dependent subjects suffering from nicotine dependence have a higher prevalence of nearly all psychiatric and addictive disorders [97], making treatment for smoking cessation in this specific population a unmet need.

In summary, we found that the current criteria of eligibility applied in clinical trial involving nicotine dependent individuals are highly restrictive, and exclude a majority of participants, thus limiting the generalizability of their findings. Particularly, our findings suggested that (1) individuals smoking few cigarettes in a day or (2) having a current or past history of mood disorders (major depressive disorder or bipolar disorder) are underrepresented in clinical trials. These two related groups should be the focus of further investigations.

## Declaration of interest

None.

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non-exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in Tobacco Control and any other BMJPGL products to exploit all subsidiary rights, as set out in our licence.

## Acknowledgments

The National Epidemiologic Survey on Alcohol and Related Conditions was sponsored by the National Institute on Alcohol Abuse and Alcoholism and funded, in part, by the Intramural Program of DHHS-NIH-NIAAA.

YLS is funded by a grant from the Société Française de Tabacologie and the Addiction Program of CAMH.

**Table 1. Eligibility criteria in 54 randomized clinical trials assessing pharmacotherapies for smoking cessation**

| Eligibility criteria present in more than 10% of the studies (ranked by frequency) | Studies using the criteria [reference number] | Number of studies using the criteria N=54 |
|---|---|---|
| 1. Pregnancy | [37, 38, 43-48, 50-54, 56, 58-65, 67-69, 71-82, 84, 98, 99] | 40 |
| 2. Cardiovascular disorder | [37, 38, 41-46, 48, 49, 51-53, 58-62, 64, 65, 67-69, 71-76, 78-82, 84, 85, 92, 98, 99] | 38 |
| 3. Smoking at least 10 cigarettes per day on average | [37-49, 53-56, 58-63, 66, 67, 69-74, 76, 78, 79, 83, 89, 92] | 37 |
| 4. Currently/past 6 months take any psychotropic medication | [38, 39, 42, 45, 47, 49, 52-54, 56, 58-60, 62-64, 66-72, 74-76, 78, 79, 81, 82, 89] | 32 |
| 5. Alcohol dependence | [38, 40-44, 47, 48, 50, 53, 54, 58-60, 62-65, 68, 70-72, 74-76, 78, 79, 81, 82, 86] | 30 |
| 6. Motivated to quit | [37-39, 43, 44, 46, 48-51, 54, 55, 58, 59, 61, 63, 65, 67, 69, 71-73, 76, 78, 79, 81, 82, 87, 98] | 29 |
| 7. Dependence to other drugs | [38, 40-44, 50, 54, 58-60, 62-66, 68, 70-72, 74-76, 78, 79, 81, 82] | 27 |
| 8. Having a current depression | [37, 38, 40-43, 45-49, 52, 54, 55, 59, 63, 66, 70, 73, 74, 76, 77] | 22 |
| 9. Currently/past 6 months take Bupropion and/or NRT | [39-43, 46, 51-55, 58, 59, 61, 63, 64, 66, 69, 78, 81, 87] | 21 |
| 10. Eating disorder | [37-39, 41-44, 47-49, 52, 54, 55, 59, 63, 66, 70, 73, 74, 76] | 20 |
| 11. Having a current psychosis | [37, 38, 40-43, 47-49, 52, 59, 63, 66, 70, 73, 74, 76, 77, 86] | 19 |
| 12. Bipolar disorder | [37, 38, 40-43, 47-49, 52, 59, 63, 66, 70, 73, 74, 76, 77] | 18 |
| 13. Having current Panic disorder | [37, 38, 40-43, 47-49, 59, 63, 66, 70, 73, 74, 76, 77] | 17 |
| 14. Using any form of tobacco other than cigarettes | [38, 40, 42, 46, 48, 53, 59-61, 64, 71, 74, 75, 79, 82, 87] | 16 |
| 15. Age less than 75 yo | [38, 40-45, 60, 62, 69, 74-77, 81, 99] | 16 |
| 16. Renal disease | [37-39, 41-46, 48, 49, 55, 59, 92] | 14 |
| 17. History/risk of seizure | [39, 41, 43, 44, 46-49, 52, 54, 55, 59, 63] | 13 |

| | | |
|---|---|---|
| 18. High blood pressure | [41-45, 48, 49, 51, 59, 68, 69, 72, 81] | 13 |
| 19. Liver disease | [37-39, 41-46, 48, 49, 55, 92] | 13 |
| 20. Skin disorder | [58, 60, 62, 67, 69, 71, 73, 74, 76, 77, 79, 80, 82] | 13 |
| 21. Neurological disease | [37-39, 41, 44, 48, 49, 55, 59, 92] | 10 |
| 22. Peptic ulcer disease | [45, 51, 59, 68, 71, 72, 80, 84, 99] | 9 |
| 23. Diabetes | [9, 13, 22-24, 35, 38, 51, 53] | 9 |
| 24. High alveolar carbon monoxide level | [53, 55, 56, 70, 74, 76] | 6 |
| 25. Allergies | [43, 48, 52, 65, 69, 70] | 6 |
| | | |
| Studies who did not reported any inclusion/exclusion criteria | [55-59] | 5 |

**Table 2. Estimated percentage of adults with nicotine dependence in the NESARC excluded from typical clinical trials of treatments for nicotine dependence by traditional efficacy eligibility criteria**

| Exclusion Variable | Current nicotine dependence (N=4,962) % (95% CI) | Motivated to quit smoking sample (N=4,121) % (95% CI) |
|---|---|---|
| Traditional efficacy exclusion criteria[a] | | |
| 1. Pregnancy | 3.19 (2.67-3.80) | 3.46 (2.89-4.13) |
| 2. Cardiovascular disorder | 6.84 (5.99-7.80) | 6.66 (5.77-7.68) |
| 3. Smoking less than 10 cigarettes per day on average | 32.02 (29.98-34.14) | 33.79 (31.79-35.85) |
| 4. Currently/past 6 months take any psychotropic medication | NA | NA |
| 5. High alcohol consumption/alcohol abuse | 13.55 (12.27-14.82) | 12.96 (11.73-14.30) |
| 6. Not motivated to quit | 17.60 (16.18-19.11)_ | 0.00 |
| 7. Use/abuse of other drugs | 3.40 (2.83-4.07) | 3.24 (2.64-3.98) |
| 8. Having a current depression | 16.62 (15.41-17.92) | 15.71 (14.41-17.10) |
| 9. Currently/past 6 months take Bupropion and/or NRT | NA | NA |
| 10. Eating disorder | NA | NA |
| 11. History of psychosis | 2.14 (1.72-2.67) | 1.95 (1.52-2.51) |
| 12. History of bipolar disorder | 10.33 (9.13-11.66) | 9.81 (8.59-11.18) |
| | | |
| Exclusion by any criterion | 65.89 (64.13-67.60) | 58.60 (56.57-60.61) |

[a] Derived from the review of 54 randomized controlled clinical trials (method described in the paper).

Percentages are weighted values

NA: Information not available in the NESARC

## References


[1] Fiore MC, Jaén CR, Baker TB. Treating Tobacco Use and Dependence: 2008 Update. *US Dept of Health and Human Services* 2008.

[2] Le Foll B, George TP. Treatment of tobacco dependence: integrating recent progress into practice. *CMAJ* 2007;**177**(11):1373-1380.

[3] Le Foll B, Melihan-Cheinin P, Rostoker G, *et al.* Smoking cessation guidelines: evidence-based recommendations of the French Health Products Safety Agency. *Eur Psychiatry* 2005;**20**(5-6):431-441.

[4] National Institute for Clinical Excellence. Brief interventions and referral for smoking cessation in primary care and other settings. Public Health Intervention Guidance No. 1, London: NICE 2006.

[5] Weisberg HI, Hayden VC, Pontes VP. Selection criteria and generalizability within the counterfactual framework: explaining the paradox of antidepressant-induced suicidality? *Clin Trials* 2009;**6**(2):109-118.

[6] Dzewaltowski DA, Estabrooks PA, Klesges LM, *et al.* Behavior change intervention research in community settings: how generalizable are the results? *Health Promot Int* 2004;**19**(2):235-245.

[7] Kamholz BW, Gulliver SB, Helstrom A, *et al.* Implications of participant self-selection for generalizability: who participates in smoking laboratory research? *Subst Use Misuse* 2009;**44**(3):343-356.

[8] Weiss NS, Koepsell TD, Psaty BM. Generalizability of the results of randomized trials. *Arch Intern Med* 2008;**168**(2):133-135.

[9] Dhruva SS, Redberg RF. Variations between clinical trial participants and Medicare beneficiaries in evidence used for Medicare national coverage decisions. *Arch Intern Med* 2008;**168**(2):136-140.

[10] Blanco C, Olfson M, Goodwin R, *et al.* Generalizability of clinical trial results for major depression to community samples: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry* 2008;**69**(8):1276-1280.

[11] Zimmerman M, Chelminski I, Posternak MA. Generalizability of antidepressant efficacy trials: differences between depressed psychiatric outpatients who would or would not qualify for an efficacy trial. *Am J Psychiatry* 2005;**162**(7):1370-1372.

[12] Zimmerman M, Mattia JI, Posternak MA. Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice? *Am J Psychiatry* 2002;**159**(3):469-473.

[13] Posternak MA, Zimmerman M, Keitner GI, *et al.* A reevaluation of the exclusion criteria used in antidepressant efficacy trials. *Am J Psychiatry* 2002;**159**(2):191-200.

[14] Zetin M, Hoepner CT. Relevance of exclusion criteria in antidepressant clinical trials: a replication study. *J Clin Psychopharmacol* 2007;**27**(3):295-301.

[15] Boter H, Derks EM, Fleischhacker WW, *et al.* Generalizability of the results of efficacy trials in first-episode schizophrenia: comparisons between subgroups of participants of the European First Episode Schizophrenia Trial (EUFEST). *J Clin Psychiatry* 2009.

[16] Leucht S, Heres S, Hamann J, *et al.* Methodological issues in current antipsychotic drug trials. *Schizophr Bull* 2008;**34**(2):275-285.

[17] Khan AY, Preskorn SH, Baker B. Effect of study criteria on recruitment and generalizability of the results. *J Clin Psychopharmacol* 2005;**25**(3):271-275.

[18] Blanco C, Olfson M, Okuda M, *et al.* Generalizability of clinical trials for alcohol dependence to community samples. *Drug Alcohol Depend* 2008;**98**(1-2):123-128.

[19] Humphreys K, Weingardt KR, Harris AH. Influence of subject eligibility criteria on compliance with National Institutes of Health guidelines for inclusion of women, minorities, and children in treatment research. *Alcohol Clin Exp Res* 2007;**31**(6):988-995.

[20] Humphreys K, Weingardt KR, Horst D, *et al.* Prevalence and predictors of research participant eligibility criteria in alcohol treatment outcome studies, 1970-98. *Addiction* 2005;**100**(9):1249-1257.

[21] Humphreys K, Weisner C. Use of exclusion criteria in selecting research subjects and its effect on the generalizability of alcohol treatment outcome studies. *Am J Psychiatry* 2000;**157**(4):588-594.

[22] Okuda M, Hasin DS, Olfson M, *et al.* Generalizability of clinical trials for cannabis dependence to community samples. *Drug Alcohol Depend* in press.

[23] Andrews JA, Severson HH, Akers L, *et al.* Who enrolls in a self-help cessation program for smokeless tobacco? *Addict Behav* 2001;**26**(5):757-764.

[24] Graham AL, Bock BC, Cobb NK, *et al.* Characteristics of smokers reached and recruited to an internet smoking cessation trial: a case of denominators. *Nicotine Tob Res* 2006;**8 Suppl 1**:S43-48.

[25] Howard-Pitney B, Fortmann SP, Killen JD. Generalizability of findings from a chewing tobacco cessation clinical trial. *Nicotine Tob Res* 2001;**3**(4):347-352.

[26] Hughes JR. Data to estimate the similarity of tobacco research samples to intended populations. *Nicotine Tob Res* 2004;**6**(1):177-179.

[27] Hughes JR, Callas PW. Data to assess the generalizability of samples from studies of adult smokers. *Nicotine Tob Res* 2009.

[28] Robinson ML, Schroeder JR, Moolchan ET. Adolescent smokers screened for a nicotine replacement treatment trial: correlates of eligibility and enrollment. *Nicotine Tob Res* 2006;**8**(3):447-454.

[29] Schmelzle J, Rosser WW, Birtwhistle R. Update on pharmacologic and nonpharmacologic therapies for smoking cessation. *Can Fam Physician* 2008;**54**(7):994-999.

[30] Fagerstrom KO. Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. *Addict Behav* 1978;**3**(3-4):235-241.

[31] Grant BF, Dawson DA, Stinson FS, *et al.* The Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV): reliability of alcohol consumption, tobacco use, family history of depression and psychiatric diagnostic modules in a general population sample. *Drug Alcohol Depend* 2003;**71**(1):7-16.

[32] Grant BF, Dawson DA, Stinson FS, *et al.* The 12-month prevalence and trends in DSM-IV alcohol abuse and dependence: United States, 1991-1992 and 2001-2002. *Drug Alcohol Depend* 2004;**74**(3):223-234.

[33] Gorwood P. Clinical assessment in psychiatric genetics. In: Leboyer M, Bellivier F, eds. *Psychiatric Genetics: Methods and Protocols*: John M. Walker, Humana Press Inc 2003:99-126.

[34] Grant B, Hasin D, Chou S, *et al.* Nicotine dependence and psychiatric disorders in the United States: results from the national epidemiologic survey on alcohol and related conditions. *Arch Gen Psychiatry* 2004;**61**(11):1107-1115.

[35] Grant BF, Harford TC, Dawson DA, *et al.* The Alcohol Use Disorder and Associated Disabilities Interview schedule (AUDADIS): reliability of alcohol and drug modules in a general population sample. *Drug Alcohol Depend* 1995;**39**(1):37-44.

[36] Eisenberg MJ, Filion KB, Yavin D, *et al.* Pharmacotherapies for smoking cessation: a meta-analysis of randomized controlled trials. *CMAJ* 2008;**179**(2):135-144.

[37] Tsai ST, Cho HJ, Cheng HS, *et al.* A randomized, placebo-controlled trial of varenicline, a selective alpha4beta2 nicotinic acetylcholine receptor partial agonist, as a new therapy for smoking cessation in Asian smokers. *Clin Ther* 2007;**29**(6):1027-1039.

[38] Nakamura M, Oshima A, Fujimoto Y, *et al.* Efficacy and tolerability of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, in a 12-week, randomized, placebo-controlled, dose-response study with 40-week follow-up for smoking cessation in Japanese smokers. *Clin Ther* 2007;**29**(6):1040-1056.

[39] Fossati R, Apolone G, Negri E, *et al.* A double-blind, placebo-controlled, randomized trial of bupropion for smoking cessation in primary care. *Arch Intern Med* 2007;**167**(16):1791-1797.

[40] Oncken C, Gonzales D, Nides M, *et al.* Efficacy and safety of the novel selective nicotinic acetylcholine receptor partial agonist, varenicline, for smoking cessation. *Arch Intern Med* 2006;**166**(15):1571-1577.

[41] Nides M, Oncken C, Gonzales D, *et al.* Smoking cessation with varenicline, a selective alpha4beta2 nicotinic receptor partial agonist: results from a 7-week, randomized, placebo- and bupropion-controlled trial with 1-year follow-up. *Arch Intern Med* 2006;**166**(15):1561-1568.

[42] Jorenby DE, Hays JT, Rigotti NA, *et al.* Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA* 2006;**296**(1):56-63.

[43] Gonzales D, Rennard SI, Nides M, *et al.* Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA* 2006;**296**(1):47-55.

[44] Holt S, Timu-Parata C, Ryder-Lewis S, *et al.* Efficacy of bupropion in the indigenous Maori population in New Zealand. *Thorax* 2005;**60**(2):120-123.

[45] Cooper TV, Klesges RC, Debon MW, *et al.* A placebo controlled randomized trial of the effects of phenylpropanolamine and nicotine gum on cessation rates and postcessation weight gain in women. *Addict Behav* 2005;**30**(1):61-75.

[46] Dalsgareth OJ, Hansen NC, Soes-Petersen U, *et al.* A multicenter, randomized, double-blind, placebo-controlled, 6-month trial of bupropion hydrochloride sustained-release tablets as an aid to smoking cessation in hospital employees. *Nicotine Tob Res* 2004;**6**(1):55-61.

[47] Collins BN, Wileyto EP, Patterson F, *et al.* Gender differences in smoking cessation in a placebo-controlled trial of bupropion with behavioral counseling. *Nicotine Tob Res* 2004;**6**(1):27-37.

[48] Aubin HJ, Lebargy F, Berlin I, *et al.* Efficacy of bupropion and predictors of successful outcome in a sample of French smokers: a randomized placebo-controlled trial. *Addiction* 2004;**99**(9):1206-1218.

[49] Tonnesen P, Tonstad S, Hjalmarson A, *et al.* A multicentre, randomized, double-blind, placebo-controlled, 1-year study of bupropion SR for smoking cessation. *J Intern Med* 2003;**254**(2):184-192.

[50] Glavas D, Rumboldt M, Rumboldt Z. Smoking cessation with nicotine replacement therapy among health care workers: randomized double-blind study. *Croat Med J* 2003;**44**(2):219-224.

[51] Shiffman S, Dresler CM, Hajek P, *et al.* Efficacy of a nicotine lozenge for smoking cessation. *Arch Intern Med* 2002;**162**(11):1267-1276.

[52] Hall SM, Humfleet GL, Reus VI, *et al.* Psychological intervention and antidepressant treatment in smoking cessation. *Arch Gen Psychiatry* 2002;**59**(10):930-936.

[53] Glover ED, Glover PN, Franzon M, *et al.* A comparison of a nicotine sublingual tablet and placebo for smoking cessation. *Nicotine Tob Res* 2002;**4**(4):441-450.

[54] Ahluwalia JS, Harris KJ, Catley D, *et al.* Sustained-release bupropion for smoking cessation in African Americans: a randomized controlled trial. *JAMA* 2002;**288**(4):468-474.

[55] Gonzales DH, Nides MA, Ferry LH, *et al.* Bupropion SR as an aid to smoking cessation in smokers treated previously with bupropion: a randomized placebo-controlled study. *Clin Pharmacol Ther* 2001;**69**(6):438-444.

[56] Wallstrom M, Nilsson F, Hirsch JM. A randomized, double-blind, placebo-controlled clinical evaluation of a nicotine sublingual tablet in smoking cessation. *Addiction* 2000;**95**(8):1161-1171.

[57] Garvey AJ, Kinnunen T, Nordstrom BL, *et al.* Effects of nicotine gum dose by level of nicotine dependence. *Nicotine Tob Res* 2000;**2**(1):53-63.

[58] Tonnesen P, Paoletti P, Gustavsson G, *et al.* Higher dosage nicotine patches increase one-year smoking cessation rates: results from the European CEASE trial. Collaborative European Anti-Smoking Evaluation. European Respiratory Society. *Eur Respir J* 1999;**13**(2):238-246.

[59] Jorenby DE, Leischow SJ, Nides MA, *et al.* A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 1999;**340**(9):685-691.

[60] Hughes JR, Lesmes GR, Hatsukami DK, *et al.* Are higher doses of nicotine replacement more effective for smoking cessation? *Nicotine Tob Res* 1999;**1**(2):169-174.

[61] Hays JT, Croghan IT, Schroeder DR, *et al.* Over-the-counter nicotine patch therapy for smoking cessation: results from randomized, double-blind, placebo-controlled, and open label trials. *Am J Public Health* 1999;**89**(11):1701-1707.

[62] Daughton D, Susman J, Sitorius M, *et al.* Transdermal nicotine therapy and primary care. Importance of counseling, demographic, and participant selection factors on 1-year quit rates. The Nebraska Primary Practice Smoking Cessation Trial Group. *Arch Fam Med* 1998;**7**(5):425-430.

[63] Hurt RD, Sachs DP, Glover ED, *et al.* A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med* 1997;**337**(17):1195-1202.

[64] Hjalmarson A, Nilsson F, Sjostrom L, *et al.* The nicotine inhaler in smoking cessation. *Arch Intern Med* 1997;**157**(15):1721-1728.

[65] Blondal T, Franzon M, Westin A. A double-blind randomized trial of nicotine nasal spray as an aid in smoking cessation. *Eur Respir J* 1997;**10**(7):1585-1590.

[66] Schneider NG, Olmstead R, Nilsson F, *et al.* Efficacy of a nicotine inhaler in smoking cessation: a double-blind, placebo-controlled trial. *Addiction* 1996;**91**(9):1293-1306.

[67] Paoletti P, Fornai E, Maggiorelli F, *et al.* Importance of baseline cotinine plasma values in smoking cessation: results from a double-blind study with nicotine patch. *Eur Respir J* 1996;**9**(4):643-651.

[68] Hall SM, Munoz RF, Reus VI, *et al.* Mood management and nicotine gum in smoking treatment: a therapeutic contact and placebo-controlled study. *J Consult Clin Psychol* 1996;**64**(5):1003-1009.

[69] Stapleton JA, Russell MA, Feyerabend C, *et al.* Dose effects and predictors of outcome in a randomized trial of transdermal nicotine patches in general practice. *Addiction* 1995;**90**(1):31-42.

[70] Schneider NG, Olmstead R, Mody FV, *et al.* Efficacy of a nicotine nasal spray in smoking cessation: a placebo-controlled, double-blind trial. *Addiction* 1995;**90**(12):1671-1682.

[71] Kornitzer M, Boutsen M, Dramaix M, *et al.* Combined use of nicotine patch and gum in smoking cessation: a placebo-controlled clinical trial. *Prev Med* 1995;**24**(1):41-47.

[72] Herrera N, Franco R, Herrera L, *et al.* Nicotine gum, 2 and 4 mg, for nicotine dependence. A double-blind placebo-controlled trial within a behavior modification support program. *Chest* 1995;**108**(2):447-451.

[73] Gourlay SG, Forbes A, Marriner T, *et al.* Double blind trial of repeated treatment with transdermal nicotine for relapsed smokers. *BMJ* 1995;**311**(7001):363-366.

[74] Hurt RD, Dale LC, Fredrickson PA, *et al.* Nicotine patch therapy for smoking cessation combined with physician advice and nurse follow-up. One-year outcome and percentage of nicotine replacement. *JAMA* 1994;**271**(8):595-600.

[75] Hjalmarson A, Franzon M, Westin A, *et al.* Effect of nicotine nasal spray on smoking cessation. A randomized, placebo-controlled, double-blind study. *Arch Intern Med* 1994;**154**(22):2567-2572.

[76] Fiore MC, Kenford SL, Jorenby DE, *et al.* Two studies of the clinical effectiveness of the nicotine patch with different counseling treatments. *Chest* 1994;**105**(2):524-533.

[77] Westman EC, Levin ED, Rose JE. The nicotine patch in smoking cessation. A randomized trial with telephone counseling. *Arch Intern Med* 1993;**153**(16):1917-1923.

[78] Tonnesen P, Norregaard J, Mikkelsen K, *et al.* A double-blind trial of a nicotine inhaler for smoking cessation. *JAMA* 1993;**269**(10):1268-1271.

[79] Sachs DP, Sawe U, Leischow SJ. Effectiveness of a 16-hour transdermal nicotine patch in a medical practice setting, without intensive group counseling. *Arch Intern Med* 1993;**153**(16):1881-1890.

[80] Effectiveness of a nicotine patch in helping people stop smoking: results of a randomised trial in general practice. Imperial Cancer Research Fund General Practice Research Group. *BMJ* 1993;**306**(6888):1304-1308.

[81] Sutherland G, Stapleton JA, Russell MA, *et al.* Randomised controlled trial of nasal nicotine spray in smoking cessation. *Lancet* 1992;**340**(8815):324-329.

[82] Tonnesen P, Norregaard J, Simonsen K, *et al.* A double-blind trial of a 16-hour transdermal nicotine patch in smoking cessation. *N Engl J Med* 1991;**325**(5):311-315.

[83] Daughton DM, Heatley SA, Prendergast JJ, *et al.* Effect of transdermal nicotine delivery as an adjunct to low-intervention smoking cessation therapy. A randomized, placebo-controlled, double-blind study. *Arch Intern Med* 1991;**151**(4):749-752.

[84] Killen JD, Fortmann SP, Newman B, *et al.* Evaluation of a treatment approach combining nicotine gum with self-guided behavioral treatments for smoking relapse prevention. *J Consult Clin Psychol* 1990;**58**(1):85-92.

[85] Hall SM, Tunstall CD, Ginsberg D, *et al.* Nicotine gum and behavioral treatment: a placebo controlled trial. *J Consult Clin Psychol* 1987;**55**(4):603-605.

[86] Hjalmarson AI. Effect of nicotine chewing gum in smoking cessation. A randomized, placebo-controlled, double-blind study. *JAMA* 1984;**252**(20):2835-2838.

[87] Hughes JR, Gust SW, Keenan RM, *et al.* Nicotine vs placebo gum in general medical practice. *JAMA* 1989;**261**(9):1300-1305.

[88] Jamrozik K, Fowler G, Vessey M, *et al.* Placebo controlled trial of nicotine chewing gum in general practice. *Br Med J (Clin Res Ed)* 1984;**289**(6448):794-797.

[89] Jarvik ME, Schneider NG. Degree of addiction and effectiveness of nicotine gum therapy for smoking. *Am J Psychiatry* 1984;**141**(6):790-791.

[90] Jarvis MJ, Raw M, Russell MA, *et al.* Randomised controlled trial of nicotine chewing-gum. *Br Med J (Clin Res Ed)* 1982;**285**(6341):537-540.

[91] Malcolm RE, Sillett RW, Turner JA, *et al.* The use of nicotine chewing gum as an aid to stopping smoking. *Psychopharmacology (Berl)* 1980;**70**(3):295-296.

[92] Schneider NG, Jarvik ME, Forsythe AB, *et al.* Nicotine gum in smoking cessation: a placebo-controlled, double-blind trial. *Addict Behav* 1983;**8**(3):253-261.

[93] Leeman RF, Huffman CJ, O'Malley SS. Alcohol history and smoking cessation in nicotine replacement therapy, bupropion sustained release and varenicline trials: a review. *Alcohol Alcohol* 2007;**42**(3):196-206.

[94] Lutsenko H, Doran CM, Hall WD. Australian smokers' use of bupropion and nicotine replacement therapies and their relation to reimbursement, Australia 2001-05. *Drug Alcohol Rev* 2008;**27**(2):160-164.

[95] Hudson JI, Hiripi E, Pope HG, Jr., *et al.* The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. *Biol Psychiatry* 2007;**61**(3):348-358.

[96] Hurt RD, Offord KP, Croghan IT, *et al.* Mortality following inpatient addictions treatment. Role of tobacco use in a community-based cohort. *JAMA* 1996;**275**(14):1097-1103.

[97] Le Strat Y, Ramoz N, Gorwood P. In alcohol-dependent drinkers, what does the presence of nicotine dependence tell us about psychiatric and addictive disorders comorbidity? *Alcohol Alcohol* 2010;**45**(2):167-172.

[98] Abelin T, Buehler A, Muller P, *et al.* Controlled trial of transdermal nicotine patch in tobacco withdrawal. *Lancet* 1989;**1**(8628):7-10.

[99] Fortmann SP, Killen JD, Telch MJ, *et al.* Minimal contact treatment for smoking cessation. A placebo controlled trial of nicotine polacrilex and self-directed relapse prevention: initial results of the Stanford Stop Smoking Project. *JAMA* 1988;**260**(11):1575-1580.